 doi:10.20944/preprints202206.0014.v1

Review

Microbial Degradation of Pharmaceuticals

Kandhasamy Swathi., Balraj Sudha., Kanagaraj Suganya and Sundaravadivelu Sumathi*

Department of Biochemistry, Biotechnology and Bioinformatics, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore-641043, TamilNadu, India
* Correspondence: author: sumathi_bc@avinuty.ac.in

Abstract: Pharmaceutically active compounds and organic pollutants are becoming a major environmental dispute possessing serious threat to the water bodies and terrestrial ecosystem. Microorganisms are capable of the self-purification process, and hence the microbial degradation is considered a lucrative method to counteract the therapeutic and recalcitrant pollutants. Pharmaceutical toxicants in aquatic system can be treated by conventional wastewater treatment, but slow sludge settling, presence of mixture of pharmaceuticals and recalcitrant compounds often pose a potential ecological risk. Some microbial strains are very effective in reducing the chemical oxygen demand (COD), biological oxygen demand (BOD), total dissolved solids (TDS), and turbidity in pharmaceutical industrial wastewater treatment. The natural microbial community has a significant role in the ecological processes of pharmaceutical and organic compounds, including non-steroidal anti-inflammatory drugs, analgesics, blood lipid regulators and other micropollutants. Specific bacterial isolates can act as biodegraders, and fungal treatment could offer protection to the ecosystem. These microorganisms use the pollutants as their sole carbon source and transform the contaminants by co-metabolic pathways. Natural attenuation by native microorganisms, biostimulation and bioaugmentation are the processes employed to degrade the target contaminant. Microorganisms may also be genetically engineered to improve the neutralization efficiency, which would assist in the mineralization of the pollutants. Thus, employing microorganisms to detoxify the pollutants probably enhances the sustainable potential biodegradability, improves water quality standards and ensures eco-friendly alternative bioremediation strategy.

Keywords: Pharmaceutical toxicants; recalcitrant pollutants; co-metabolic pathways; biostimulation; bioaugmentation

Introduction

Pharmaceuticals aids in the fundamental treatment of the public health and its degradation is becoming an environmental dispute in the form of pollutants. Management of pharmaceutical contaminants including used and expired products, personal home-care products, and over the counter medications have become as the biggest global health challenge (Woolridge and Hoboy, 2019). The pharmaceutical contaminants hit the atmosphere through multiple ways. Mostly the unmetabolized medical excipients are subjected to sewage for conventional or biological treatment plants (Teixeira *et al.*, 2016). This treatment modality is not equipped to treat water contaminated with trace levels of pharmaceuticals present, and it may be considered largely ineffective in removing them. Incineration, mechanical disruption, encapsulation, chemical sterilization, alkaline hydrolysis are some waste treatment technologies which are highly undesirable and toxic (Blenkharn, 2011). The unorganized disposal of contaminated, used and expired pharmaceutical products possesses a serious threat to the aquatic and landfill ecosystem. Although various regulatory bodies and support in the management of hazardous, non-hazardous and chemo wastes, conservation of the environment from pharmaceutically active pollutants is a great challenge. The uncontrolled long-term exposure of these active pollutants, even in trace level negatively influences the aquatic and surface habitat (Barnes *et al.*, 2008). The packaging of medicinal products is mainly made-up of plastics and metals

 doi:10.20944/preprints202206.0014.v1

which also unfeasible to dispose or recover (Wang *et al.,* 2015). The pharmaceutical residues and biocides including antibiotics, analgesics, antimicrobials, anticonvulsants, beta-blockers, antihistamines, lipid regulators, antipsychotic, genotoxic wastes, infectious, pathological wastes, synthetic hormones and bulk pharmaceutical contaminants should be safely removed from ecosystem for a harmless environment (Sreedhar, 2018). Majority of the conventional treatment methods have limited scope, high-cost and also time consuming.

Microorganisms are major organic matter and xenobiotic degraders, like pharmaceuticals, and helps to maintain the proper functioning of ecosystem (Singh, 2011). Once pharmaceuticals hit the ecosystem, processes such as biodegradation, photodegradation, hydrolysis and sorption into suspended solids and bed sediments are involved to determine the ecotoxicity (Yamamoto *et al.,* 2009; Liang *et al.,* 2013). Photodegradation and microbial-mediated degradation methods are effectively employed to remove the toxic pharmaceutical compounds in the environment. Microbial degradation is the most significant dissipation pathway for pharmaceuticals in the environment (Fang *et al.,* 2012) and the degradation rate depends on the temperature, pH, richness of microorganisms and the amount of biosolids and lipophilicity of the pharmaceuticals (Monteiro and Boxall, 2009). Microorganisms can degrade pollutants through metabolic and co-metabolic or enzymatic pathways and hence they play a role in protection and regulation of ecosystem. Recovery from contamination is only possible, if the toxic effects of the molecules do not impede microflora. Microorganisms like *Rhodococcus rhodochrous, Pseudomonas putida, Pseudomonas fluorescens, Bacillus subtilis, Aspergillus niger* and *Sphingomonas herbicidovorans*, white rot fungus *Phanerochaete chrysosporium* and genera *Pseudomonas, Arthrobacter*, and *Enterobacter* have been reported to reduce the toxic effects of pharmaceutically active contaminants with the help of certain co-substrates like carbon source (Gauthier *et al.,* 2010). Studies involving series batch culture of the aerobic and unsaturated compounds have also shown pharmaceutical degradation of ibuprofen and diclofenac (Tiehm *et al.,* 2011).

Due to the eco-friendly behaviour of microorganisms, exploring advancements in microbial techniques has a broad range assistance in degradation of bioactive solid and liquid pharma pollutants. The review mainly focusses on the fundamental aspects and application of microorganisms as biodegraders for the complete mineralization of pharmaceutically active toxic compounds.

Mechanism of biodegradation

The two main biodegradation forms are known to be hydrolysis and biological oxidation. Based on the sources used, such as enzymes or bacteria, these mechanisms are further divided. The transformation of xenobiotics by microorganisms occurs by growth and co-metabolic processes. Growth process uses organic pollutant as the sole carbon energy for the complete mineralization of organic contaminants. In presence of growth substrate like carbon, the organic pollutants are metabolized, which is termed as co-metabolism (Jørgensen, 2008). Bacteria, fungi, yeast and certain protozoa are involved in degradation of active pollutants. The core advantage of this process is enhancement of complete mineralization of the organic compounds into carbondioxide and water, which occurs either aerobically or anaerobically (Fritsche and Hofrichter, 2008).

There are three phases of biodegradation -1) Natural attenuation involves reduction of pollutants by natural microorganisms 2) Biostimulation is a technique to improve the biodegrading efficiency by providing nutrients and oxygen to the process 3) Bioaugmentation, where more efficient supplementary microorganisms are added to the system in addition to natural microflora to target the specific contaminants (Diez, 2010). Microorganisms are affected by a number of factors to use organic pollutants as substrate or to co-metabolize them, such as, pH, temperature, nitrogen and phosphorus content, which influences the rate and extent of degradation (Fritsche and Hofrichter, 2008). Biodegradation methods are essentially a vital process using natural flora to transform the active therapeutic pollutants like drugs and other medical wastes.

 doi:10.20944/preprints202206.0014.v1

Pharmaceuticals in the environment:

Pharmaceuticals have lifesaving credits, but the removal of pharmaceutical wastes and its by-products are of an emerging threat to the ecosystem. The harmful effect of pharmaceutical compounds on habitats can be known from advanced analytical techniques like GC-MS/MS, LC-MS/MS, UPLC/MS, which determines certain adverse issues of pharmaceuticals in the environment, present in micro and nanogram quantities (Larsson, 2014; Daughton, 2004). These therapeutically activated compounds are considered to be pseudopersistent because of their prolonged infusion into the ecological matrix amidst their simultaneous degradation by various process and thus triggers the formation of intricate pharmaceutical pool (Stackelberg *et al.*, 2004). Waste water treatment plants do not completely remove pharmaceuticals since they are normally equipped to handle organic products in the milligram range, that are quickly and moderately degradable (Le-Minh *et al.*, 2010; Ziylan and Ince, 2011). Pharmaceutical products vary from most other contaminants on the basis of: (a) molecular masses lesser than 500 Da, but larger for some compounds (Lipinski *et al.*, 1997) (b) chemically complex molecules comprising a wide range of structures, shapes, molar mass and function (c) polar compounds having more than one ionizable category (d) Properties and degrees of ionisation that are dependent on the pH of the medium (e) lipophilic and (f) mild water solubility g) these molecules have a propensity to adsorb and be dispersed in a living body, which changes their chemical structure metabolically (Kümmerer, 2009; Tahar *et al.*, 2013). "Over the counter medications" caused uncertainity in the consumption and usage estimates, leading to tons of active pharmaceutical compounds in the environment (Greiner and Rönnefahrt, 2003). Many pharmaceutical compounds hit the aquatic environment. These therapeutic compounds have been grouped by Bush (1997) as i) anti-inflammatory and analgesic agents (ibuprofen, paracetamol, diclofenac); (ii) antibiotics (sulfonamides, tetracyclines, penicillins, β-lactams, macrolides, fluoroquinolones, imidazoles); (iii) anti-epileptic agents (carbamazepines); (iv) anti-depressants (benzodiazepines); (v) lipid-lowering agents (fibrates); (vi) Antihistamines (famotidine, ranitidine); (vii) β-blockers (metoprolol, atenolol, propranolol); and other substances (viii) (barbiturates, narcotics, antiseptics, and contrast media) (Rivera-Utrilla *et al.*, 2013). Most environmental pharmaceutical occurrences have identified pollutant groups including hospital effluents, effluents and sewage treatment system, surface water, groundwater and drinking water (Patel *et al.*, 2019). Microbial biodegradation of pharmaceuticals is particularly essential especially when wastewater treatment and sewage treatment plants are inefficient.

Microbial transformation of pharmaceuticals:

Microbial cells are the perfect choice for transformation of pollutants, owing to some factors like high surface-volume ratio, reduction in the time of biomass transformation, higher metabolic rate and easy maintenance of sterility (Coelho and Ribeiro, 2015; Hegazy *et al.*, 2015). The factors influencing the biotransformation of contaminants include incubation period of microorganisms and the chemical structure and properties of pharmaceutical products.

Antibiotics

Most pharmaceuticals are toxic to bacteria and some naturally occurring bacteria have the ability to biodegrade the active pollutants. Antibiotics are antimicrobials that are used to inhibit and treat microbial infection. These are secondary metabolites of bacterial and fungal origin, or from semi-synthetic natural products or synthetic (Fair and Toy, 2014). The persistent occurrence and release of antibiotics in the aquatic and land may increase the resistance towards microbes. Furthermore, the absence or reluctance of organic matter and chemical catalytic microorganisms in waste water treatment plants and soil, may be another significant problem associated with antibiotic survival (Polianciuc *et al.*, 2020). In order to develop new, updated and enhanced antibiotics with characteristics

 doi:10.20944/preprints202206.0014.v1

such as minimal toxicity, wide antimicrobial range, improved oral adsorption, less conferring resistance effects, the microbial transformation of existing antibiotics has been carried out. Sulfonamide antibiotics have bacteriostatic effect and sulfamethazine concentrations of 0.6 ng/L were reported to be present in groundwater. Sulfamethazine in soils can affect the soil respiration and natural microbial communities (Kotzerke *et al.,* 2008). A study showed the field employment of Gram-positive Micro bacterium sp. strain was able to mineralize benzylic and pyrimidine molecule of sulfamethazine. Sulfadiazine is a sulfonamide antibiotic, that is partially mineralized by *Microbacterium lacus* strain SDZm4 (Tappe *et al.,* 2013). The PR1 strain of *Achromobacter denitrificans* can degrade the sulfonamide class drugs such as sulfasalazine, sulfamethazine, sulfamethoxypyridazine, sulfapyridine, sulfamethoxine and sulfathiazole (Reis *et al.*, 2014). *Rhodococcus rhodochrous* showed a 20% decrease in concentrations of sulfamethizole and sulfamethoxazole. *Bacillus megaterium* can produce a bioconversion product lankacidin-C-14-butyrate from lankacidin C and methyl-butyrate can enhance the antimicrobial efficiency with reduced side effects (Smitha *et al.,* 2017). Several sulfonamides, ciprofloxacin and norfloxacin can be degraded by the enzymes of White-rot fungus (Rodríguez-Rodríguez *et al.,* 2012; Prieto *et al.,* 2011; Rodarte-Morales *et al.*, 2012). The fungi *Trametes versicolor* can eliminate sulfapyridine, sulfathiazole and ofloxacin. Ofloxacin is a fluoroquinolone antibiotic, which when treated with *Trametes versicolor* in Erlenmeyer flask, could undergo 80% degradation (Gros *et al.*, 2014). Enrofloxacin and other antibiotics can be transformed by *Basidomycetes indogenous* (Wetzstein *et.al.*, 2006). *Trichoderma harzianum* by a co-metabolic decomposition resulted in 72% degradation of clarithromycin (Buchicchio *et al.*, 2016). Fluoroquinolone (FQ) antibiotics ofloxacin, norfloxacin, and ciprofloxacin gets degraded by *Labrys portucalensis F11* and *Pseudoxanthomonas* in culture medium in presence of carbon. Biotransformation by *Labrys portucalensis* occur by cleavage of the piperazine ring and fluorine substituent replacement allow intermediate formation with less antibacterial toxicity. *Microbacterium* sp. is able to biotransform norfloxacin to metabolites like 8-hydroxynorfloxacin, 6-defluoro-6-hydroxynorfloxacin, desethylene norfloxacin and N-acetylnorfloxacin (Kim *et al.,* 2011). These microorganisms could be used in bioaugmentation processes to increase the performance of contaminant removal in wastewater treatment plants.

Anti-inflammatory and analgesic agents

Non-steroidal anti-inflammatory drugs (NSAIDs) are pain-relief medications that contain narcotics and are used to alleviate pain in nearly all diseases. Naproxen, ibuprofen, diclofenac, ketoprofen, aspirin are some of the pharmacologically active NSAIDs (Marco-Urrea *et al.,* 2010a; Marco-Urrea *et al.,* 2010b; Marco-Urrea *et al.,* 2010c). Studies indicating that, Ibuprofen was observed to be more active than the parent molecule and the initial concentration of biodegradation using river water microbial biofilms was found to be 100 µg/L and the degradation occurs within 5 to 10 days of the initial addition (Winkler *et al.,* 2001). In liquid media, *Nocardia sp., α-Proteobacteria* and Sphingomonas sp. were able to degrade 500 mg/L of ibuprofen with carbon as the energy source (Murdoch and Hay, 2013). Ibuprofen degradation by microorganisms like cyanobacteria considerably diminished together with *Gamma-Proteobacteria* and Gram-positive bacteria *Firmicutes*, while *α-β-Proteobacteria, Cytophaga-Flavobacteria* and sulfate-reducing bacteria amplified the biodegradation process. The *Spingomonas* strain degrades ibuprofen by cleavage of isobutylocatechol by ibuprofen-CoA ligase, hydroxylation and ferredoxin reductase enzymes. Removal of acidic side chain of ibuprofen is enhanced by the meta ring cleavage and also it is the characteristic for ibuprofen degradation by *Variovorax* Ibu-1 (Murdoch and Hay 2015). *Bacillus thuringiensis B1* and *Patulibacter medicamentivorans* (Marchlewicz *et al.*, 2017b; Salgado *et al.,* 2020) were also reported for ibuprofen degradation.

Pseudomonas and *Penicillium* strain degrade high level of paracetamol into 4-aminophenol with the complete elimination of acetate (Hart and Orr, 1975). *Pseudomonas moorei*

 doi:10.20944/preprints202206.0014.v1

KB4, Stenotrophomonas sp. f1, Pseudomonas sp. f2, Pseudomonas sp. fg-2 (Żur *et al.,* 2018b; Zhang *et al.,* 2013), *Bacillus aryabhattai strain 1-Sj-5-2-5-M, Bacillus subtilis strain HJ5* and *Klebsiella pneumonia strain S001* (Liang *et al.,* 2016) are known to act as paracetamol degraders. *Cunninghamella echinulate* can metabolize paracetamol into N-acetyl-p-benzoquinoneimine by hydroxylation and rearrangement mechanism (RatnaKumari *et al.,* 2009). *Trametes versicolor* completely transforms ketoprofen by cytochrome P450 enzymatic transport with 2-([3-hydroxy(phenyl)methyl] phenyl)-propanoic acid and 2-[3-(4- hydroxybenzoyl)phenyl]-propanoic acid and 2-(3-benzoyl-4-hydroxyphenyl)-propanoic acid as the major metabolites (Marco-Urrea *et al.,* 2010b).

Pseudomonas putida was effective in removal of salicylic acid (Zhang *et al.,* 2013; Combarros *et al.*, 2014) and the degradation mechanism under aerobic condition by microorganism involves i) hydroxylation into catechol or gentisate or ring cleavage into 2-oxo-3,5-heptadienedioic acid by NADH-independent salicylate 1,2- dioxygenase (Hintner *et al.,* 2001). ii) the cleavage of gentisic acid results in maleylpyruvate and fumarylpyruvate formation (Lowe-Power *et al.,* 2016). In presence of *Rhodococcus* and *Streptococcus sp.,* salicylate is converted into gentisate by AMP ligase. It leads to salicylyl-CoA formation, where it is hydroxylated to gentisyl-CoA and latter to maleylpyruvate formation, which is notable for central degradation mechanism (Ishiyama *et al.,* 2004; Marchlewicz *et al.,* 2015). Four types of white-rot fungi (*Irpex lacteus, Phanerochaete chrysosporium, Ganoderma lucidium,* and *Trametes versicolor*) were able to cleave ibuprofen within 10days of addition. Complete mineralization of Ibuprofen can be achieved by all the above white-rot fungi with hydroxylated derivative like 1,2-Dihyroxyibuprofen as the main end product (Marco-Urrea *et al.*, 2009).

In a bioreactor, *Phanerochaete chrysosporium* completely eliminated NSAIDs upto 95.6%. *Phanerochaete sordida can catalyze* diclofenac to 4′-hydroxydiclofenac, 5-hydroxydiclofenac and 4′,5-dihydroxydiclofenac by oxidation co-metabolized by cytochrome P450, manganese peroxidase and laccase with an elimination efficacy of about 90% (Hata *et al.,* 2010). The strain *Enterobacter hormaechei D15* and *Klebsiella sp.* KSC strain were reported to transform high concentrations of ibuprofen (Stylianou *et al.,* 2018). Naproxen degradation by *Aspergillus niger* follows hydroxylation mechanism of cytochrome system with O-desmethylnaproxen, 7-hydroxynaproxen and 7-hydroxy-O-desmethylnaproxen as the byproducts (He and Rosazza 2003).

The fluorobiphenyl-containing medication flurbiprofen can be degraded by biphenyl-degrading *Pseudomonas pseudoalcaligenes* KF707 into hydroxylated metabolite (Green *et al.,* 1999; Murphy *et al.,* 2008; Hughes *et al.,* 2011) and *Cunninghamella elegans, Cunninghamella echinulate, Cunninghamella blakesleeana* and *Streptomyces* bacteria can destroy the flurbiprofen and convert it into oxidized products of fluorometabolites such as 4-hydroxyflurbiprofen, 3,4-dihydroxyflurbiprofen and hydroxyl-methoxy-flurbiprofen (Amadio *et al.,* 2010; Bright *et al.,* 2011). This detoxification mechanism can be observed in the Phase II mechanism of biotransformation. Flurbiprofen methyl ester was converted into two hydroxylated products by *E. coli* expressing cyanobacterial cytochrome P450 (CYP110E1) with a very low (5%) yield (Makino *et al.,* 2012) and incubation of the substance with dried *Aspergillus oryzae* mycelium dissolved in an organic solvent (e.g. toluene) with ethanol will overcome racemic flurbiprofen (Spizzo *et al.,* 2007). In both sterile and non-sterile settings, a fluidized bed batch reactor was used to remove pharmaceuticals and endocrine disruptors from hospital waste water using *Trametes versicolor* (Cruz-Morató *et al.*, 2014). *Chlorella sorokiniana* was also used to successfully degrade 60-100% of diclofenac, paracetamol and ibuprofen for biodegradation but the rate of salicylic acid elimination is 2.3 times greater than that of paracetamol (Escapa *et al.*, 2015; Escapa *et al.*, 2017). Dihydroxyacetone has been frequently used in cosmetics can be degraded by *Gluconobacter melanogenus* (Gupta *et al.,* 2001) and Prostaglandins (PGE2) undergoes microbial transformation with *Cryptococcus neoformans* (Tsitsigiannis *et al.,* 2005).

 doi:10.20944/preprints202206.0014.v1

Anticonvulsant or Anti-epileptic drugs

Carbamazepine and Gabapentin, used for treating seizures is reported as the recurring drugs in surface and ground water and the degradation of such compounds is a typical process. Since Gabapentin is difficult to metabolise in biota, the biological excretion rate is extremely large. Frequent existence of Gabapentin and Carbamazepine in aquatic environments raises worries about the ecosystem. *Rhodococcus rhodochrous* and *Aspergillus Niger* was reported to be significant in degradation of carbamazepine in presence of glucose. Cunninghamella elegans was also found as bio degrader of carbamazepine in liquid medium and 60-80% removal of carbamazepine was achieved by *Phanerochaete chrysosporium* in a non-sterile bioreactor when employed for over 100 days (Zhang and Geißen, 2012). A study showed that, *Trichoderma harzianum*, which degrades carbamazepine by a co-metabolic process resulted in 57% removal and aerobic degradradation by *Trametes versicolor* gave complete mineralization of carbamazepine (94%) in six days and the rate of degradation increased upto 95.6% in the bioreactor with acridine, acridone, 10,11-epoxy-carbamazepine, and 10,11-dihydro-10,11-dihydroxycarbamazepine (Kang *et al.*, 2008) as the major end products. Bjerkandera sp. manganese peroxidase is incapable of degrading carbamazepine (Marco-Urrea *et al.*, 2009). However, carbamazepine degradation was more effective when Mn^{2+} and glucose peptone were added to the medium. *Umbelopsis ramanniana, Cunning-hamella elegans* (Kang *et al.*, 2008) and *Pleurotus ostreatus* (has peroxidase enzyme) were also able to degrade carbamazepine efficiently (Golan-Rozen *et al.*, 2011). Literature indicated that, *Scenedesmus obliquus* and *Chlamydomonas mexicana* microalgae has the potential to eliminate 28% and 35% of carbamazepine at a concentration of 1mg/L; however higher concentrations have the ability to suppress the algal growth (Xiong *et al.*, 2016).

Degradation of Anti-depressants

Antidepressants drugs helps to alleviate anxiety, dysthymia, insomnia and other related conditions. Susceptibility of antidepressants to microorganisms for drugs Prozac® (fluoxetine HCl), and the 1,4-benzodiazepine, Valium® (Diazepam) and their major human metabolites (norfluoxetine HCl, temazepam and oxazepam) in bacterial liquid cultures from sewage sludge (SS)-soil amendments studies could gave an insight on degradation of anti-depressant drugs. In liquid culture experiments carried out for 60 days, and even after extended exposure in SS-soil amendment (fluoxetine HCl), the pharmaceuticals were reported to be immune to biodegradation. In liquid culture investigations, oxazepam has been the only 1,4-benzodiazepine that could undergo biotic transition and also 80% loss was reported under abiotic and biotic aspects (Redshaw *et al.*, 2008). Fluoxetine (Prozac) is an antidepressant with a trifluoromethylphenyl moiety that is normally prescribed and citalopram (another fluorinated antidepressant) can undergo microbial degradation by Bjerkandera sp. R1, Bjerkandera adjusta and *Phanerochaete chrysosporium* (Rodarte-Morales *et al.*, 2012). These three species were able to fully degraded citalopram (1 mg/l) during 14 days treatment time, but fluoxetine was only slightly degraded, reaching a limit of 46% in culture of the anamorph of Bjerkandera *sp. R1*. In presence of low concentrations (2 M) of substrate, the bacterium *L. portucalensis* F11 can degrade fluoxetine, resulting in molar quantities of fluoride ion (Moreira *et al.*,2014) and in presence of carbon source, acetate, large amount of fluoxetine can undergo degradation.

Lipid-lowering agents (fibrates)

Lipid abnormalities are key risk factors for cardio vascular disease, and reducing cholesterol concentrations of low-density lipoprotein (LDL) can substantially reduce the incidence of heart disease. Statins and fibrates are the two major groups of lipid-lowering agents (Lawrence *et al.*,2005). Gemfibrozil is a cholesterol regulating drug prescribed to patients with coronary heart disease (Veach *et al.*,2012) and the drug is metabolized by the liver and excreted via urine as an aglucuronide conjugate (Christen *et al.*,2010). This

 doi:10.20944/preprints202206.0014.v1

glucuronide was found to be biodegraded by the fungus *Cunninghamella elegans* (Russell *et al.*,2004). Study on *Trametes versicolor* reported that, it degraded 10milligram of clofibric acid at about 97% within 7days of treatment and *Ganderma lucidium* showed 47% removal of clofibric acid, which produced 4-chlorophenolate, 2-hydroxymethacrylic acid and hydroxy-clofibric acid as the key products (Marco-Urrea *et al.*,2009). Atorvastatin is one of the commonly prescribed medicines to reduce the lipid level, but only a few microbial degradation methods are available. There has been no research data on the bacterial degradation of this compound, however Rodríguez-Rodríguez *et al.,* (2012) studied the role of white-rot fungus *T. versicolor* for atorvastatin degradation. T. versicolor when grown on a sterile sludge, reduction in atorvastatin was reported. Although no *invitro studies* were performed, laccase activity from *T. versicolor* was suggested as an important factor in the pharmaceutical's biodegradation process.

Antihistamines

For several years, antihistamines have been a breakthrough in the treatment of allergic diseases. The oxidative deamination activity of certain microorganisms degrades histamine by catalyzing histamine oxidase or histamine dehydrogenase. *Rummeliibacillus stabekisii*, *Agrobacterium tumefaciens, Bacillus cereus, Bacillus polymyxa, Bacillus licheniformis, Bacillus amyloliquefaciens, Bacillus subtilis, Bacillus licheniformis*, were the 8-bateria isolated from salted fish products to degrade histamines. However, in contrast to the other isolates, *B. polymyxa* had the highest activity in degrading histamine in liquid broth media by producing histamine dehydrogenase (Lee *et al.,* 2015). *Lactobacillus plantarum* D-103 is a histamine degrading bacteria reported to have 100% degradation (Kung *et al.,* 2017). Histamine and tyramine could get degraded by *Staphylococcus xylosus* (Mah and Hwang, 2009).

β-blockers (metoprolol, atenolol, propranolol)

Beta blockers are a type of drug that is used to treat irregular heart rhythms and are known as beta-adrenergic blocking agents. White-rot fungus can degrade propranolol and atenolol by its ligninolytic enzymes, peroxidases, laccases, and intracellular enzymes (Asgher *et al.*, 2008) and with the process of formylation, hydroxylation, dehalogenation, and deamination reactions, it can degrade the contaminants. *Trametes versicolor* degraded β-blockers in a fluidized bed bioreactor for 8 days, in both sterile and nonsterile wastewater (Cruz-Morató *et al.*, 2013).

Other substances

Antiseptics are biocides that are used to inhibit the growth of microorganisms, but they are not antibiotics. Antiseptics or preservatives in clinical environments, cosmetics, household cleaning products, plastic materials, toys, paints, and other consumer products all contain triclosan and also triclosan is related to change in normal endocrine function in humans (Carr *et al.*,2011). The bacterium from activated sludge namely Nitrosomonas europaea, and the β- proteobacterial, Methylobacillus sp. were found to biodegrade triclosan in liquid culture media (Murdoch and Hay, 2005). *Pseudomonas putida TriRY* and *Alcaligenes xylosoxidans subsp. denitrificans TR1* have high triclosan resistance (0.4 mg/L) and can use it as their only carbon source (Meade *et al.*,2001). Diatrizoate and Iopromide are contrasting agents in X-rays that can be degraded by the powerful oxidation enzymes of White-rot fungus (Rode and Muller, 1998).

Conclusion

Pharmaceuticals have been in the atmosphere for a long time, but their adverse effects have only been discovered in the last two and a half decades. These contaminants are typically unable to be completely eliminated by main and secondary water treatment therapies, resulting in their migration into drinking water sources. Biotransformation's are changes in the structure of a chemical compound caused by microorganisms/enzyme

 doi:10.20944/preprints202206.0014.v1

systems, which could result in the creation of molecules with a higher polarity or results in complete mineralization of such compounds. Biodegradation is highly useful for dealing with real-world environmental concerns like pharmaceuticals and personal care products. New pharmaceuticals are emerging continuously due to raising health ailments. Therefore, accurate and advanced degrading techniques involving microorganisms can be standardized for all kinds of pharmaceuticals with greater degrading ability that could help to preserve the natural ecosystem.

References:

Amadio, J., & Murphy, C.D. (2010). Biotransformation of fluorobiphenyl by *Cunninghamella elegans*. *Applied Microbiology and Biotechnology*. 86:345-351.

Asgher, M., Bhatti, H. N., Ashraf, M., Legge, R. L. (2008). Recent Developments in Biodegradation of Industrial Pollutants by White Rot Fungi and Their Enzyme System. *Biodegradation*, 19, 771– 771, doi: 10.1007/s10532-008-9185-3

Barnes, K. K., Kolpin, D. W., Furlong, E. T., Zaugg, S. D., Meyer, M. T., Barber, L. B. (2008). A National Reconnaissance of Pharmaceuticals and Other Organic Wastewater Contaminants in the United States, Groundwater. *Science* of the *Total Environment*. 402, 192-200.

Blenkharn, J.I., (2011). Clinical Waste Management, Blenkharn Environmental, Elsevier B.V, London, UK.

Buchicchio, A., Bianco, G., Sofo, A., Masi, S., Caniani, D. (2016). Biodegradation of Carbamazepine and Clarithromycin by *Trichoderma Harzianum* and *Pleurotus Ostreatus* Investigated by Liquid Chromatography-High-Resolution Tandem Mass Spectrometry (Fticr Ms-Irmpd). *Science* of the *Total Environment* . 557:733-739, doi: 10.1016/j.scitotenv.2016.03.119

Bush, K. (1997). Antimicrobial Agents. *Current Opinion in Chemical Biology*. 1, 169-175, doi: 10.1016/S1367-5931(97)80006-3

Carr, D. L., Morse, A. N., Zak, J. C., & Anderson, T. A. (2011). Biological degradation of common pharmaceuticals and personal care products in soils with high water content. *Water, Air, & Soil Pollution*, *217*(1), 127-134.

Christen, V., Hickmann, S., Rechenberg, B., & Fent, K. (2010). Highly active human pharmaceuticals in aquatic systems: a concept for their identification based on their mode of action. *Aquatic toxicology*, *96*(3), 167-181.

Coelho, M.A., & Ribeiro, B.D. (2015). White Biotechnology for Sustainable Chemistry. UK: RCS publishing.

Combarros, R., Rosas, I., Lavín, A., Rendueles, M., Díaz, M. (2014). Influence of Biofilm on Activated Carbon on the Adsorption and Biodegradation of Salicylic Acid in Wastewater. *Water, Air, & Soil Pollution*, 225, 1858. doi: 10.1007/s11270-013-1858-9

Cruz-Morató, C., Ferrando-Climent, L., Rodriguez-Mozaz, S., Barceló, D., Marco-Urrea, E., Vicent, T., & Sarrà, M. (2013). Degradation of pharmaceuticals in non-sterile urban wastewater by Trametes versicolor in a fluidized bed bioreactor. *Water research*, 47(14), 5200-5210.

Cruz-Morató, C., Lucas, D., Llorca, M., Rodriguez-Mozaz, S., Gorga, M., Petrovic, M., Barceló, D., Vicent, T., Sarrà, M., Marco-Urrea, E. (2014). Hospital Wastewater Treatment by Fungal Bioreactor: Removal Efficiency for Pharmaceuticals and Endocrine Disruptor Compounds. *Science of the Total Environment*. 493, 365-376, doi: 10.1016/j.scitotenv.2014.05.117

Daughton, C. G. (2004). Non-regulated water contaminants: emerging research. Environmental Impact Assessment Review, 24(7-8), 711-732.

Diez, M. C. (2010). Biological aspects involved in the degradation of organic pollutants. Journal of soil science and plant nutrition, 10(3), 244-267.

Escapa, C., Coimbra, R. N., Paniagua, S., García, A. I., & Otero, M. (2017). Paracetamol and salicylic acid removal from contaminated water by microalgae. *Journal of Environmental Management*, *203*, 799-806.

Escapa, C., Coimbra, R. N., Paniagua, S., García, A. I., & Otero, M. (2015). Nutrients and pharmaceuticals removal from wastewater by culture and harvesting of Chlorella sorokiniana. *Bioresource Technology*, *185*, 276-284.

Fair, R. J., & Tor, Y. (2014). Antibiotics and bacterial resistance in the 21st century. *Perspectives in medicinal chemistry*, 6, 25–64. https://doi.org/10.4137/PMC.S14459

Fang, Y., Karnjanapiboonwong, A., Chase, D. A., Wang, J., Morse, A. N., & Anderson, T. A. (2012). Occurrence, fate, and persistence of gemfibrozil in water and soil. Environmental toxicology and chemistry, 31(3), 550-555.

Fritsche, W., and Hofrichter, M. (2008). Aerobic Degradation by Microorganisms, Second Edition, Wiley-VCH Verlag GmbH, Weinheim, Germany.

Gauthier, H., Yargeau, V., & Cooper, D. G. (2010). Biodegradation of pharmaceuticals by Rhodococcus rhodochrous and Aspergillus niger by co-metabolism. Science of the Total Environment, 408(7), 1701-1706.

Golan-Rozen, N., Chefetz, B., Ben-Ari, J., Geva, J., Hadar, Y. (2011). Transformation of the Recalcitrant Pharmaceutical Compound Carbamazepine by *Pleurotus Ostreatus*: Role of Cytochrome P450 Monooxygenase and Manganese Peroxidase. *Environ. Sci. Technol.* 45, 6800– 6805, doi: 10.1021/es200298t

Green, N.A., Meharg, A.A., Till, C., Troke, J., Nicholson, J.K. (1999). Degradation of 4-fluorobiphenyl in soil investigated by F-19 NMR spectroscopy and C-14 radiolabelling analysis. *Chemosphere*, 38: 1085–1101.

Greiner, P., Rönnefahrt, I. (2003). Management of Environmental Risks in the Life Cycle of Pharmaceuticals; European Conference on Human and Veterinary Pharmaceutucals in the Environment, Lycon, April 14-16 2003.

Gros, M., Cruz-Morato, C., Marco-Urrea, E., Longrée, P., Singer, H., Sarrà, M., Hollender, J., Vicent, T., Rodriguez-Mozaz, S., Barceló, D. (2014). Biodegradation of the X-Ray Contrast Agent Iopromide and the Fluoroquinolone Antibiotic Ofloxacin by the White Rot Fungus Trametes Versicolor in Hospital Wastewaters and Identification of Degradation Products. *Water Research.* 60: 228-241, doi: 10.1016/j.watres.2014.04.042

Guleria, A., and Pradesh, H. (2014). Biodegradation of Pharmaceutical Waste, 4-Nitrophenol by *Pseudumonas Putida*. *Indian Journal of Research*, 3, 127-130.

Gupta, A., Singh, V. K., Qazi, G. N., & Kumar, A. (2001). Gluconobacter oxydans: its biotechnological applications. *Journal of molecular microbiology and biotechnology*, 3(3), 445-456.

Hart, A., & Orr, D. L. J. (1975). The degradation of paracetamol (4-hydroxyacetanilide) and other substituted acetanilides by a Penicillium species. *Antonie Van Leeuwenhoek*, 41(1), 239-247.

Hata, T., Kawai. S., Okamura, H., Nishida, T. (2010). Removal of diclofenac and mefenamic acid by the white rot fungus *Phanerochaete sordida* YK-624 and identification of their metabolites after fungal transformation. *Biodegradation.* 21:681-689. doi: 10.1007/s10532-010-9334-3

He, A., & Rosazza, J.P. (2003). Microbial transformations of S-naproxen by *Aspergillus niger* ATCC 9142. *Pharmazie,* 58:420-2. doi:10.1002/chin.200339085

Hegazy, M. E. F., Mohamed, T. A., ElShamy, A. I., Abou-El-Hamd, H. M., Mahalel, U. A., Reda, E. H., ... & Hammouda, F. M. (2015). Microbial biotransformation as a tool for drug development based on natural products from mevalonic acid pathway: A review. *Journal of Advanced Research*, *6*(1), 17-33.

Hintner, J.P., Lechner, C., Riegert, U., Kuhm, A.E., Storm, T., Reemtsma, T., Stolz, A. (2001). Direct ring fission of salicylate by a salicylate 1,2-dioxygenase activity from *Pseudaminobacter salicylatoxidans*. *Journal of Bacteriology*. 183(23):6936-42. doi: 10.1128/JB.183.23.6936-6942.2001

Kung, H. F., Lee, Y. C., Huang, Y. L., Huang, Y. R., Su, Y. C., & Tsai, Y. H. (2017). Degradation of histamine by *Lactobacillus plantarum* isolated from miso products. *Journal of food protection*, *80*(10), 1682-1688.

Ishiyama, D., Vujaklija, D., & Davies, J.E. (2004). Novel Pathway of Salicylate Degradation by Streptomyces sp. Strain WA46. *Applied and Environmental Microbiology, 70*, 1297 - 1306.

Jørgensen, S. E. (2008). Biodegradation. *Encyclopedia of Ecology*, *2*, 366-367.

Kang, S. I., Kang, S. Y., & Hur, H. G. (2008). Identification of fungal metabolites of anticonvulsant drug carbamazepine. *Applied microbiology and biotechnology*, *79*(4), 663-669.

Kim, D. W., Heinze, T. M., Kim, B. S., Schnackenberg, L. K., Woodling, K. A., & Sutherland, J. B. (2011). Modification of norfloxacin by a Microbacterium sp. strain isolated from a wastewater treatment plant. *Applied and environmental microbiology*, 77(17):6100-6108. https://doi.org/10.1128/AEM.00545-11

Kotzerke, A., Sharma, S., Schauss, K., Heuer, H., Thiele-Bruhn, S., Smalla, K., et al. (2008). Alterations in soil microbial activity and N-transformation processes due to sulfadiazine loads in pig-manure. Environ. Pollut. 153, 315-322. doi: 10.1016/j.envpol.2007.08.020

Kümmerer, K. (2009). Antibiotics in the Aquatic Environment- a Review-Part I. *Chemosphere* 2009, 75, 417-434. doi: 10.1016/j.chemosphere.2008.11.086

Larsson, D. J. (2014). Pollution from Drug Manufacturing: Review and Perspectives. *Philosophical Transactions of the Royal Society B*. 369. doi: 10.1098/rstb.2013.0571

Lawrence, J. R., Swerhone, G. D., Wassenaar, L. I., & Neu, T. R. (2005). Effects of selected pharmaceuticals on riverine biofilm communities. *Canadian journal of microbiology*, *51*(8), 655-669.

Le-Minh, N., Khan, S. J., Drewes, J. E., & Stuetz, R. M. (2010). Fate of antibiotics during municipal water recycling treatment processes. *Water research*, *44*(15), 4295-4323.

Liang, C., Lan, Z., Zhang, X., Liu, Y. (2016). Mechanism for the primary transformation of acetaminophen in a soil/water system. *Water Research*. 98:215-24. doi: 10.1016/j.watres.2016.04.027

Liang, X., Chen, B., Nie, X., Shi, Z., Huang, X., Li, X. (2013). The distribution and partitioning of common antibiotics in water and sediment of the Pearl River Estuary, South China. *Chemosphere*. 92:1410–1416.

Lipinski, C. A., Lombardo, F., Dominy, B. W., Feeney, P. J. (1997). Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Advanced Drug Delivery Reviews*. 23, 3-25, doi: 10.1016/S0169-409X(96)00423-1

Lowe-Power, T.M., Jacobs, J.M., Ailloud, F., Fochs, B., Prior, P., Allen.C. (2016). Degradation of the plant defense signal salicylic acid protects Ralstonia solanacearum from toxicity and enhances virulence on tobacco. mBio, 7. 10.1128/mBio.00656-16

Mah, J.H., and Hwang, H.J. (2009), Inhibition of biogenic amine formation in a salted and fermented anchovy by *Staphylococcus xylosus* as a protective culture, *Food Control*, 20, 796-801.

Marchlewicz, A., Guzik, U. & Wojcieszyńska, D. (2015). Over-the-Counter Monocyclic Non-Steroidal Anti-Inflammatory Drugs in Environment-Sources, Risks, Biodegradation. *Water Air Soil Pollution* 226:355. https://doi.org/10.1007/s11270-015-2622-0

Marchlewicz, A., Guzik, U., Smułek, W., & Wojcieszyńska, D. (2017). Exploring the degradation of ibuprofen by *Bacillus thuringiensis* B1(2015b): the new pathway and factors affecting degradation, *Molecules*, 22.

Marco-Urrea, E., Aranda, E., Caminal, G., Guillén, F. (2009). Induction of Hydroxyl Radical Production in *Trametes Versicolor* to Degrade Recalcitrant Chlorinated Hydrocarbons. *Bioresour.Technol.* 100, 5757-5762. 10.1016/j.biortech.2009.06.078

Marco-Urrea, E., Radjenović, J., Caminal, G., Petrović, M., Vicent, T., Barceló, D. (2010). Oxidation of Atenolol, Propranolol, Carbamazepine and Clofibric Acid by a Biological Fenton-Like System Mediated by the White-Rot Fungus Trametes Versicolor. *Water Research*. 2010, 44, 521-532. doi: 10.1016/j.watres.2009.09.049

Marco-Urrea, E., Pérez-Trujillo, M. Cruz-Morató, C., Caminal, G., Vicent, T. (2010b). White-Rot Fungus-Mediated Degradation of the Analgesic Ketoprofen and Identification of Intermediates by HPLC-DAD-MS and NMR. *Chemosphere* 2010b, 78, 474-481. doi: 10.1016/j.chemosphere.2009.10.009

Marco-Urrea, E., Pérez-Trujillo, M., Cruz-Morató, C., Caminal, G., Vicent, T. (2010c). Degradation of the Drug Sodium Diclofenac by *Trametes Versicolor* Pellets and Identification of Some Intermediates by NMR. The *Journal of Hazardous Materials*. 176, 836-842, doi: 10.1016/j.jhazmat.2009.11.112

Meade, M. J., Waddell, R. L., & Callahan, T. M. (2001). Soil bacteria Pseudomonas putida and Alcaligenes xylosoxidans subsp. denitrificans inactivate triclosan in liquid and solid substrates. *FEMS Microbiology Letters*, 204(1), 45-48.

Monteiro, S.C., Boxall, A.B. (2009). Factors affecting the degradation of pharmaceuticals in agricultural soils. Environmental Toxicology and Chemistry. 28:2546–2554.

Moreira, I.S., Ribeiro, A.R., Afonso, C.M., Tiritan, M.E., Castro, P.M.L. (2014). Enantioselective biodegradation of fluoxetine by the bacterial strain Labrys portucalensis F11. *Chemosphere*, 111:103–111

Murdoch, R. V & Hay, A.G. (2005). Formation of catechols via removal of acid side chains from ibuprofen and related aromatic acids, *Applied and Environmental Microbiology*. 71:6121-6125.

Murdoch, R.W., & Hay, A.G. (2013). Genetic and chemical characterization of ibuprofen degradation by Sphingomonas Ibu-2. *Microbiology*. 159:621-632.

Murdoch, R.W., & Hay, A.G. (2015). The biotransformation of ibuprofen to trihydroxyibuprofen in activated sludge and by Variovorax Ibu-1. Biodegradation, 26:105-113.

Murphy, C.D., Quirke, S., & Balogun, O. (2008). Degradation of fluorobiphenyl by Pseudomonas pseudoalcaligenes KF707. FEMS microbiology letters, 286(1), 45-49.

Patel, M., Kumar, R., Kishor, K., Mlsna, T., Pittman Jr, C. U., & Mohan, D. (2019). Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chemical reviews, 119(6), 3510-3673.

Polianciuc, S. I., Gurzău, A. E., Kiss, B., Ştefan, M. G., & Loghin, F. (2020). Antibiotics in the environment: causes and consequences. Medicine and pharmacy reports, 93(3), 231-240. https://doi.org/10.15386/mpr-1742

Prieto, A., Möder, M., Rodil, R., Adrian, L., Marco-Urrea, E. (2011). Degradation of the Antibiotics Norfloxacin and Ciprofloxacin by a White-Rot Fungus and Identification of Degradation Products. *Bioresource Technology*. 102, 10987-10995. doi: 10.1016/j.biortech.2011.08.055

RatnaKumari, T., Vidyavathi, M., Asha, S., & Prasad, K. (2009). Biotransformation of Paracetamol by *Cunninghamella echinulata*. *Journal of Pharmaceutical Research, 8*, 1-5.

Redshaw, C.H., Cooke, M.P., Talbot, H.M. *et al.* (2008). Low biodegradability of fluoxetine HCl, diazepam and their human metabolites in sewage sludge-amended soil. *Journal of Soils and Sediments*, 217. https://doi.org/10.1007/s11368-008-0024-2

Reis, P. J. Reis, A. C., Ricken, B., Kolvenbach, B. A., Manaia, C. M., Corvini, P. F., Nunes, O. C. (2014). Biodegradation of Sulfamethoxazole and Other Sulfonamides by *Achromobacter Denitrificans* Pr1. *Journal of Hazardous Materials*. 280, 741-749, doi: 10.1016/j.jhazmat.2014.08.039

Riser-Roberts E. (1998). Remediation of petroleum contaminated soils. Biological, physical, and chemical process. Lewis Publishers Inc (ed). CRC Press LLC. USA. 1-542.

Rivera-Utrilla, J., Sánchez-Polo, M., Ferro-García, M. Á., Prados-Joya, G., Ocampo-Pérez, R. (2013). Pharmaceuticals as Emerging Contaminants and Their Removal from Water. A Review. *Chemosphere*, 93, 1268-1287, doi: 10.1016/j.chemosphere.2013.07.059

Rodarte-Morales, A., Feijoo, G., Moreira, M., Lema, J. (2012). Operation of Stirred Tank Reactors (STRs) and Fixed-Bed Reactors (FBRs) with Free and Immobilized *Phanerochaete Chrysosporium* for the Continuous Removal of Pharmaceutical Compounds. *Biochemical Engineering Journal,* 66, 38-45, doi: 10.1016/j.bej.2012.04.011

Rode, U., & Mu̎ller, R. (1998). Transformation of the ionic X-ray contrast agent diatrizoate and related triiodinated benzoates by Trametes versicolor. *Applied and environmental microbiology,* 64(8), 3114-3117.

Rodríguez-Rodríguez, C. E., Barón, E., Gago-Ferrero, P., Jelić, A., Llorca, M., Farré, M., Díaz-Cruz, M. S., Eljarrat, E., Petrović, M., Caminal, G. (2012). Removal of Pharmaceuticals, Polybrominated Flame Retardants and UV-Filters from Sludge by the Fungus Trametes Versicolor in Bioslurry Reactor. *Journal of Hazardous Materials*, 233, 235-243. doi: 10.1016/j.jhazmat.2012.07.024

Russell, A.D. (2004), Whither triclosan, *Journal of Antimicrobial Chemotherapy*. 53:693–695.

Salgado, R., Brito, D., Noronha, J.P., Almeida, B., Bronze, M.R., Oehmen, A., Carvalho, G., Barreto Crespo, M.T. (2020). Metabolite identification of ibuprofen biodegradation by Patulibacter medicamentivorans under aerobic conditions, *Environmental Technology*, 41:450-465.

Singh, S. N. (2011). Microbial degradation of xenobiotics. Springer Science & Business Media.

Smitha, M.S., Singh, S., Singh, R., (2017). Microbial bio transformation: a process for chemical alterations, *Journal of Bacteriology & Mycology*. 4(2):47-51. doi: 10.15406/jbmoa.2017.04.00085

Sreedhar, A., Apte, M., Rashmi (2018). Pharmaceutical waste management. Mallya, *International Journal of Pharmaceutical Sciences Review and Research*,52(1).

Stackelberg, P. E., Furlong, E. T., Meyer, M. T., Zaugg, S. D., Henderson, A. K., Reissman, D. B. (2004). Persistence of Pharmaceutical Compounds and Other Organic Wastewater Contaminants in a Conventional Drinking-Water-Treatment Plant. *Science of the Total Environment*. 329, 99-113. doi: 10.1016/j.scitotenv.2004.03.015

Stylianou, K., Hapeshi, E., Vasquez, M.I., Fatta-Kassinos, D., Vyrides, I. (2018). Diclofenac biodegradation by newly isolated *Klebsiella* sp. KSC: microbial intermediates and ecotoxicological assessment. *Journal of Environmental Chemical Engineering*. 6:3242-3248. doi: 10.1016/j.jece.2018.04.052

Tahar, A., Choubert, J.-M., Coquery, M. (2013). Xenobiotics Removal by Adsorption in the Context of Tertiary Treatment: A Mini Review. *Environmental Science* and *Pollution Research*. 20, 5085-5095, doi: 10.1007/s11356-013-1754-2

Tappe, W., Herbst, M., Hofmann, D., Koeppchen, S., Kummer, S., Thiele, B., & Groeneweg, J. (2013). Degradation of sulfadiazine by Microbacterium lacus strain SDZm4, isolated from lysimeters previously manured with slurry from sulfadiazine-medicated pigs. *Applied and environmental microbiology*, 79(8), 2572-2577. https://doi.org/10.1128/AEM.03636-12

Teixeira, S., Gurke, R., Eckert, H., *et al.*,(2016). Photocatalytic degradation of pharmaceuticals present in conventional treated wastewater by nanoparticle suspensions. *Journal of Environmental Chemical Engineering*, 4(1):287–292.

Tiehm, A., Schmidt, N., Stieber, M., Sacher, F., Wolf, L., Hoetzl, H. (2011). Biodegradation of phmaceutical compounds and their occurrence in the Jordan valley. *Water Resources Management*. 25(4):1195-1203

Tsitsigiannis, D.I., Bok, J.W., Andes, D., Nielsen, K.F., Frisvad, J.C., Keller, N.P. (2005). Aspergillus cyclooxygenase-like enzymes are associated with prostaglandin production and virulence. *Infection and Immunity* . 73(8):4548-59. doi: 10.1128/IAI.73.8.4548-4559.2005

Veach,A., Bernot, M.J., Mitchell, J.K. (2012). The influence of six pharmaceuticals on freshwater sediment microbial growth incubated at different temperatures and UV exposures, *Biodegradation*, 23:497–507.

Wang, C., Wang, H., Liu, Y. (2015). Separation of aluminum and plastic by metallurgy method for recycling waste pharmaceutical blisters. *Journal of Cleaner Production*. 102, 2015, 378-383.

Wetzstein, H.-G., Schneider, J., Karl, W. (2006). Patterns of Metabolites Produced from the Fluoroquinolone Enrofloxacin by Basidiomycetes Indigenous to Agricultural Sites. *Applied Microbiology and Biotechnology*, 2006, 71, 90-100. doi: 10.1007/s00253-005-0178-4

Winkler, M., Lawrence, J. R., & Neu, T. R. (2001). Selective degradation of ibuprofen and clofibric acid in two model river biofilm systems. *Water Research*, *35*(13), 3197-3205.

Woolridge, A., & Hoboy, S. (2019). Medical Waste. In Waste, Academic Press, 517-530.

Xiong, J.-Q., Kurade, M. B., Abou-Shanab, R. A., Ji, M.-K., Choi, J., Kim, J. O., Jeon, B.-H. (2016). Biodegradation of Carbamazepine Using Freshwater Microalgae *Chlamydomonas Mexicana* and *Scenedesmus Obliquus* and the Determination of its Metabolic Fate. *Bioresource Technology*. 205, 183-190, doi: 10.1016/j.biortech.2016.01.038

Yamamoto, H., Nakamura, Y., Moriguchi, S., Nakamura, Y., Honda, Y., Tamura, I., Hirata, Y., Hayashi, A., Sekizawa, J. (2009). Persistence and Partitioning of Eight Selected Pharmaceuticals in the Aquatic Environment: Laboratory Photolysis, Biodegradation, and Sorption Experiments. *Water* Research. 43, 351– 362.

Lee, Y. C., Lin, C. S., Liu, F. L., Huang, T. C., & Tsai, Y. H. (2015). Degradation of histamine by Bacillus polymyxa isolated from salted fish products. Journal of food and drug analysis, 23(4), 836-844.

Zhang, L., Hu, J., Zhu, R., Zhou, Q., Chen, J. (2013). Degradation of Paracetamol by Pure Bacterial Cultures and Their Microbial Consortium. *Applied Microbiology and Biotechnology*. 97, 3687-3698. doi: 10.1007/s00253-012-4170-5

Zhang, Y., & Geißen, S.-U. (2012). Elimination of Carbamazepine in a Non-Sterile Fungal Bioreactor. *Bioresource Technology*. 112, 221– 227. doi: 10.1016/j.biortech.2012.02.073

Ziylan, A., & Ince, N. H. (2011). The Occurrence and Fate of Anti-Inflammatory and Analgesic Pharmaceuticals in Sewage and Fresh Water: Treatability by Conventional and Non-Conventional Processes. *Journal of Hazardous Materials*. 2011, 187, 24-36. doi: 10.1016/j.jhazmat.2011.01.057

Żur, J., Piński, A., Marchlewicz, A., Hupert-Kocurek, K., Wojcieszyńska, D., & Guzik, U. (2018). Organic micropollutants paracetamol and ibuprofen-toxicity, biodegradation, and genetic background of their utilization by bacteria. *Environmental science and pollution research international*, 25(22), 21498-21524. https://doi.org/10.1007/s11356-018-2517-x